IN THE UNITED STATES PATENT AND TRADEMARK OFFICE



IN RE APPLICATION OF
KRIWET ET AL.
APPLICATION NO: 09/871,367
FILED: MAY 31, 2001
FOR: TOPICAL COMPOSITIONS COMPRISING ASCOMYCINS

Art Unit: 1614
Examiner: Vickie Kim

Assistant Commissioner for Patents
Washington, DC 20231

CLAIM OF PRIORITY UNDER 35 USC §119

Sir:

Applicants in the above-identified application hereby claim priority under the International Convention of Application No. 9826656.2, filed on December 3, 1998. This application is acknowledged in the Declaration of the instant case.

The certified copy of said application is submitted herewith.

Respectfully submitted,

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Date: December 18, 2001

4-30724 P1

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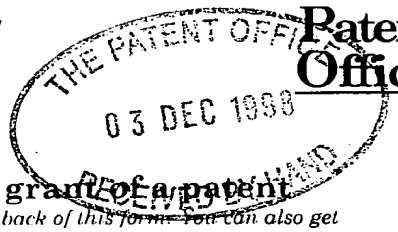


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040EC98 E409594-1 D00524
P01/7700 0.00 - 9826656.2

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| 1. | Your reference | **4-30724/P1** |
| 2. | Patent application number *(The Patent Office will fill in this part)* | **9826656.2** **03 DEC 1998** |
| 3. | Full name, address and postcode of the or of each applicant *(underline all surnames)* | **NOVARTIS AG**<br>**SCHWARZWALDALLEE 215**<br>**4058 BASEL**<br>**SWITZERLAND** |
| | Patent ADP number *(if you know it)* | 7125487002 |
| | If the applicant is a corporate body, give the country/state of its incorporation | **SWITZERLAND** |
| 4. | Title of invention | **Organic compounds** |
| 5. | Name of your agent *(If you have one)* | |
| | "Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)* | **B.A. YORKE & CO.**<br>**CHARTERED PATENT AGENTS**<br>**COOMB HOUSE, 7 ST. JOHN'S ROAD**<br>**ISLEWORTH**<br>**MIDDLESEX TW7 6NH** |
| | Patents ADP number *(if you know it)* | **1800001** |

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| 8. | Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*<br>*a) any applicant named in part 3 is not an inventor, or*<br>*b) there is an inventor who is not named as an applicant, or*<br>*c) any named applicant is a corporate body.*<br>*(see note (d))* | **Yes** |

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Organic Compounds

This invention relates to topical compositions containing ascomycins for treatment of skin disorders, particularly psoriasis.

Ascomycins have a variety of useful pharmacological actions, e.g. immunsuppression, which may be administered topically. However inter alia because of their physicochemical properties, e.g. high molecular weight and lipophilicity the ascomycins have posed problems for topical administration and until now there is no commercially available ascomycin topical composition.
Skin disorders also present difficulties in treatment, particularly psoriasis, where the skin barrier function and skin lipid composition may have changed. Topical compositions for use in psoriasis and similar diseases containing an ascomycin present particular difficulties.

After exhaustive testing the present Applicants have surprisingly found that the particular systems of the present invention serve to enhance penetration of active agent through human skin, e.g. for the treatment of psoriasis. These compositions show other particularly interesting properties, e.g. they are easily applied to large areas of the skin and are stable.

In one aspect this invention provides a composition for topical administration of an ascomycin as active agent which composition comprises a carrier vehicle comprising
(i) means to retain water in the outer skin layer, and
(ii) means to hinder water evaporating from the skin.

The active agent may be an ascomycin or a derivative thereof, e.g. a compound of the FK 506 class. FK506 is a known macrolide antibiotic that is produced by Streptomyces tsukubaensis No 9993. It is also a potent immunosuppressant. The structure of FK506 is given in the appendix to the Merck Index, 11th Edition as item A5. Methods of preparing FK506 are described in EP 184162.

A large number of derivatives, antagonists, agonists and analogues of FK506, which retain the basic structure and at least one of the biological properties (for example immunological properties) of FK506, are now known. These compounds are described in a large number of publications, for example EP 184162, EP 315978, EP 323042, EP 423714, EP 427680, EP

465426, EP 474126, WO 91/13889, WO 91/19495, EP 484936, EP 532088, EP 532089, EP 569337, EP 626385, WO 93/5059 and the like.

It is also known (for example from EP 315978 and EP 474126) that ascomycin derivatives such as macrolactam compounds of the FK506 class are extremely useful in the topical treatment of inflammatory and hyperproliferative skin diseases and of cutaneous manifestations of immunologically-mediated illnesses.

Thus examples of ascomycin derivatives suitable for use in the present invention include FK506; 33-epi-chloro-33-desoxy-ascomycin as disclosed in Example 66a in EP 427 680 (hereafter referred to as Compound A);

{[1E-(1R,3R,4R)]1R,4S,5R,6S,9R,10E,13S,15S,16R,17S,19S,20S}-9-ethyl-6,16,20-trihydroxy-4-[2-(4-hydroxy-3-methoxy-cyclohexyl)-1-methylvinyl]-15,17-dimethoxy-5,11,13,19-tetramethyl-3-oxa-22-aza-tricyclo[18.6.1.0(1,22)] heptacos-10-ene-2,8,21,27-tetraone as disclosed in Examples 6d and 71 in EP 569 337 (hereafter referred to as Compound B); and

{1R,5Z,9S,12S-[1E-(1R,3R,4R)],13R,14S,17R,18E,21S,23S,24R,25S,27R} 17-ethyl-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxy-cyclohexyl)-1-methylvinyl] -23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-aza-tricyclo[22.3.1.0(4,9)] octacosa-5,18-diene-2,3,10,16-tetraone, also known as 5,6-dehydro-ascomycin as disclosed in Example 8 in EP 626 385 (hereafter referred to as Compound C).

Ascomycins and derivatives thereof, including FK506, are referred to hereafter as "ascomycins".

The active agent is e.g. present in the compositions of this invention in an amount of from 0.05 to 3 % by weight, e.g. from 0.1 to 2 by weight, e.g. from 0.4 to 1 by weight based on the total weight of the composition.

The active agent may be dissolved, e.g. partially dissolved and/or in suspension, e.g. partially in suspension in the vehicle. Preferably the active agent may be used in a micronized form. The suspension may contain particles of ascomycin of from 5, e.g. from 10,

to about 90, preferably to about 25 microns in diameter. The particles of the ascomycin may be produced in conventional manner, e.g. by grinding or milling.

The carrier vehicle comprises means to retain water in the outer skin layer, preferably a urea, e.g. urea itself or derivatives thereof, e.g. monoacetyl urea. Urea may be present in amount of from 1 and 20 %, preferably from 5 to 15 %, more preferably about 10 % by weight based on the total weight of the composition. Urea may be in suspension in the vehicle.

Preferably the ascomycin and the means to retain water in the outer skin layer are present in a weight ratio of 0.05 to 3 : 1 to 20, more preferably in a weight ratio of 0.1 to 2 : 5 to 15, even more preferably in a weight ratio of 0.4 to 1 : about 10.

The carrier vehicle further comprises means to hinder water evaporating from the skin, e.g. hydrocarbons. Hydrocarbons may be selected from a group comprising petrolatum, e.g. white petrolatum, mineral oil, paraffin and mixtures thereof. Hydrocarbons may be present in amount of from 70 to 95 %, preferably from 75 to 90 %, more preferably about 85 % by weight based on the total weight of the composition.
The amount and the type of hydrocarbons in the composition may depend on the desired viscosity of the composition as is conventional.

Preferably the ascomycin and the hydrocarbon are present in a weight ratio of 0.05 to 3 : 70 to 95, more preferably in a weight ratio of 0.1 to 2 : 75 to 90, even more preferably in a weight ratio of 0.4 to 1 : about 85.

In another aspect the present invention provides a composition as defined above which composition comprises a carrier vehicle comprising

(i) a urea, and

(ii) a hydrocarbon.

In another aspect the present invention provides a composition as defined above which composition comprises a carrier vehicle further comprising lipophilic means to solubilize ascomycin. The lipophilic means may be selected from a group comprising isopropylmyristate; waxes; e.g. natural wax, semisynthetic wax, synthetic wax, liquid wax,

emulsifying wax and the like; fatty alcohols, saturated and/or unsaturated, branched and/or unbranched, having e.g. a $C_8$ to $C_{24}$ chain; fatty acids, saturated and/or unsaturated, branched and/or unbranched, having e.g. a $C_8$ to $C_{24}$ chain; fatty oils, comprising e.g. mono-, di- and tri- glycerides, having e.g. $C_8$ to $C_{24}$ fatty acids. The oil component may consist of one component or a mixture of components. Preferably the oil component may be isopropylmyristate. The oil component may be present in amount of from 1 to 15 %, preferably from 2 to 10 %, more preferably about 5 % by weight based on the total weight of the composition.

The lipophilic means may serve to dissolve partially the active agent. Typically 1 to 5 % of the active agent is dissolved. Preferably a saturated solution of the active agent in the composition is obtained.

Preferably the ascomycin and the lipophilic means are present in a weight ratio of 0.05 to 3 : 1 to 15, more preferably in a weight ratio of 0.1 to 2 : 2 to 10, even more preferably in a weight ratio of 0.4 to 1 : about 5.

Preferably the ascomycin, the urea, the hydrocarbon and the lipophilic means, when present, are present in a weight ratio of 0.05 to 3 : 1 to 20 : 70 to 95 : 1 to 15, more preferably in a weight ratio of 0.1 to 2 : 5 to 15 : 75 to 90 : 2 to 10, even more preferably in a weight ratio of 0.4 to 1 : about 10 : about 85 : about 5.

The components of the carrier vehicle may be described in Fiedler, H. P. "Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete", Editio Cantor Verlag Aulendorf, Aulendorf, 4th revised and expanded edition (1996), the contents of which are hereby incorporated by reference.

The compositions of this invention may be water-free or substantially water-free. The compositions may however comprise water, e.g. in an amount of from 0 to about 10 % by weight based on the total weight of the composition, e.g. from 0.5 to 5 %, e.g. from 1 to 3 %. Preferably the compositions of this invention may be water-free.

The compositions of the invention are preferably in the form of an ointment.

If desired, stabiliser agents to hinder degradation of urea may be included, e.g. allantoin, acteylglyceride, propionic acid ester, taurin, collagen, collagen hydrolysate, amino acid salts, monoalkylphosphate diethanolamine, triacetin, milk acid, polysaccharides, e.g. as described in Fiedler, H. P. (see above, page 737).
Further components, e.g. preserving agents against microorganism contamination and antioxidants, such as benzyl alcohol, butyl-hydroxytoluene, ascorbyl palmitate, sodium pyrosulphite, butyl hydroxy anisole, propyl p-hydroxybenzoate, methyl p-hydroxybenzoate, sorbic acid and tocopherol may be included as appropriate. Preserving agents and antioxidants are preferably present in an amount of about 0.01 to about 2.5 % by weight based on the total weight of the composition.
If desired, pH modifying agents may be included to bring the pH of the composition to between 4 and 6 or by adding a pharmaceutically acceptable buffer system. A pH of between 4 and 6 is desirable to avoid skin irritation.

The compositions according to the invention are useful in the treatment of inflammatory and hyperproliferative skin diseases and of cutaneous manifestations of immunologically-mediated diseases. Examples of such diseases are psoriasis, atopic dermatitis, contact dermatitis and further eczematous dermatitises, seborrhoeic dermatitis, Lichen planus, Pemphigus, bullous Pemphigoid, Epidermolysis bullosa, urticaria, angioedemas, vasculitides, erythemas, cutaneous eosinophilias, Lupus erythematous and Alopecia areata. Compositions containing an antifungal active agent may be used to treat e.g. onychomycosis.

In another aspect the present invention provides a composition as defined above for use in the treatment of inflammatory and hyperproliferative skin diseases and of cutaneous manifestations of immunologically-mediated diseases.

In another aspect the present invention provides a method for treating inflammatory and hyperproliferative skin diseases and of cutaneous manifestations of immunologically-mediated diseases comprising administering a composition as defined above to the skin of a patient in need thereof.

In yet another aspect the present invention provides the use of a composition as defined above in the preparation of a medicament for the treatment of inflammatory and

hyperproliferative skin diseases and of cutaneous manifestations of immunologically-mediated diseases.

In yet another aspect the present invention provides the use of a carrier vehicle as defined above to enhance penetration of an ascomycin through human skin.

The carrier vehicle may be in the form of an ointment.

The compositions of the invention may be prepared in a conventional manner by working up the components into a pharmaceutical composition.
For example, the composition of the invention may be obtained by suspending the ascomycin and the urea in a mixture of liquid hydrocarbons and the oil component. Solid hydrocarbons may be mixed into the suspension as conventional.
Alternatively, the composition of the invention may be obtained by suspending the ascomycin and the urea in a mixture of liquid hydrocarbons, solid hydrocarbons and the oil component as conventional. Other excipients may be added at the appropriate time to the appropriate component as is conventional.

The utility of the compositions according to the invention can be observed in standard clinical tests such as the test set out below.

A representative clinical trial is carried out as follows:
A randomised double-blind, vehicle-controlled within-patient study comparing the composition of the invention at a dose of 0.1 to 2 % by weight (based on the total weight of the composition) active agent over e.g. 10 $cm^2$, corresponding to a dose of about 0.1 to 1 $mg/cm^2$, and if desired 0.05% clobetasol-17-propionate ointment as positive control is performed in patients with chronic plaque type psoriasis.
In total 16 to 26 patients are treated with the composition twice daily for three weeks. The therapeutic effect on erythema, induration and scaling is evaluated for each of three clinical signs. In addition, the time to partial clearance is used for efficacy. Local tolerability of study medications and routine safety parameters, including haematology and clinical chemistry, are recorded.

The compositions of the invention are found to be effective.

The exact amount of the ascomycin and of the composition to be administered depends on several factors, for example the desired duration of treatment and the rate of release of the ascomycin. Satisfactory results are obtained in larger mammals, e.g. humans, with the local application over the area to be treated of a 0.1 to 2 % by weight, preferably 1 % by weight, concentration of the ascomycin once or several times a day (for example 2 to 5 times a day). In general the compositions may be applied to areas of skin as small as 1 $cm^2$ to as large as 1 $m^2$. Suitable skin loadings of the ascomycins fall within the range of 0.1 $mg/cm^2$ to 1 $mg/cm^2$.

In particular the utility of the compositions according to the invention can be observed in standard clinical tests such as the test set out in Example 1 *infra* using a concentration of 0.1 to 2 % by weight (based on the total weight of the composition) active agent.
The formulation of Example 1 was found to be effective in psoriasis compared to its corresponding vehicle without using occlusion.

The compositions of this invention are well tolerated on skin. Good skin penetration and permeation rates may be achieved using the compositions of this invention.

The compositions of this invention have the advantage of few components, are straightforward to prepare and are well-tolerated on human skin.

Following is a description by way of example only of compositions of this invention.

Example 1

An ointment is prepared having the following composition (amounts in g)

| | |
|---|---|
| Compound A | 1 |
| Urea | 10 |
| White petrolatum | 39 |
| Mineral oil | 35 |
| Paraffin | 10 |
| Isopropyl myristate | 5 |

| | |
|---|---|
| Total | 100 |

The composition is prepared by suspending Compound A and urea in mineral oil and isopropylmyristate and heating to 60°C. White petrolatum and paraffin are heated to 80°C, cooled to 60°C and slowly added to the ascomycin mixture. The composition is then cooled to room temperature. An ointment is formed.

In total 20 patients were treated for three weeks. The therapeutic effect on erythema, induration and scaling was evaluated for each of three clinical signs. In addition, the time to partial clearance was used for efficacy. Local tolerability of study medications and routine safety parameters, including haematology and clinical chemistry, were recorded.

The formulation of Example 1 was effective. Local tolerability of the study medications tested was good and no systemic side effects were observed.

Example 2

An ointment is prepared having the same composition as in Example 1.

The composition is prepared by heating mineral oil, paraffin, white petrolatum and isopropylmyristate to 80°C, cooling to 60°C and suspending Compound A and urea in the mixture obtained. The composition is then cooled to room temperature. An ointment is formed.

Compound A in the composition described in Example 1 or Example 2 may be replaced by Compound B or C.

Claims

1. A composition for topical administration of an ascomycin as active agent which composition comprises a carrier vehicle comprising

(i) means to retain water in the outer skin layer, and

(ii) means to hinder water evaporating from the skin.

2. A composition as claimed in claim 1 wherein the means to retain water in the outer skin layer is a urea.

3. A composition as claimed in claim 1 or 2 wherein the means to hinder water evaporating from the skin is a hydrocarbon.

4. A composition as claimed in claim 3 wherein the hydrocarbon is selected from a group comprising petrolatum, mineral oil, paraffin and mixtures thereof.

5. A composition as claimed in any preceding claim wherein the carrier vehicle further comprises lipophilic means to solubilize ascomycin.

6. A composition as claimed in claim 5 wherein the lipophilic means is selected from a group comprising isopropylmyristate, waxes, fatty alcohols, fatty acids, fatty oils and mixtures thereof.

7. A composition as claimed in any preceding claim wherein the ascomycin is present in an amount of 0.1 to 2.0 % by weight of the composition.

8. A composition as claimed in any preceding claim wherein the means to retain water in the outer skin layer is present in an amount of 5 to 15 % by weight of the composition.

9. Use of the carrier vehicle as claimed in claim 1 to enhance penetration of an ascomycin through human skin.

10. A composition substantially as herein described with reference to the Examples.